Alternative tumour necrosis factor inhibitors (TNFi) or abatacept or rituximab following failure of initial TNFi in rheumatoid arthritis: the SWITCH RCT

Sarah Brown,[1] Colin C Everett,[1] Kamran Naraghi,[2] Claire Davies,[1] Bryony Dawkins,[3] Claire Hulme,[3] Christopher McCabe,[4] Sue Pavitt,[5] Paul Emery,[3,6] Linda Sharples[1] and Maya H Buch[3,6]*

[1]Clinical Trials Research Unit, Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, UK
[2]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK
[3]Academic Unit of Health Economics, Leeds Institute of Health Sciences, University of Leeds, Leeds, UK
[4]Department of Emergency Medicine, University of Alberta, Edmonton, AB, Canada
[5]Dental Translational and Clinical Research Unit, University of Leeds, Leeds, UK
[6]National Institute for Health Research Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, UK

*Corresponding author m.buch@leeds.ac.uk

Declared competing interests of authors: Maya H Buch reports grants from Pfizer and Chugai Pharmaceutical Co. Ltd (Roche), and personal fees from AstraZeneca, Mitsubishi Tanabe Pharma Corporation, Bristol-Myers Squibb, Chugai Pharmaceutical Co. Ltd (Roche), Sandoz and R-Pharm, during the conduct of the study. Claire Hulme reports grants from the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme, during the conduct of the study, and was a member of the NIHR HTA Commissioning Board during the conduct of the study. Paul Emery reports grants and personal fees from Pfizer, Merck Sharp & Dohme Corp., AbbVie, Bristol-Myers Squibb, UCB Pharma Ltd, Roche, Novartis, Samsung, Sandoz, and Eli Lilly and Company, during the conduct of the study. Sue Pavitt is a member of the Efficacy and Mechanism Evaluation Board and NIHR Clinical Trials Unit Board and has been a recipient of NIHR Clinical Trials Unit Support funding. Linda Sharples, Sarah Brown and Claire Davies report grants from NIHR HTA programme during the conduct of the study. Christopher McCabe reports that historically he worked as a paid consultant for a number of pharmaceutical companies. He has also done paid extensive work for the NHS.

Published June 2018
DOI: 10.3310/hta22340

Scientific summary

The SWITCH RCT: alternative TNF-blocking drugs or abatacept or rituximab

Health Technology Assessment 2018; Vol. 22: No. 34
DOI: 10.3310/hta22340

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Rheumatoid arthritis (RA) is a chronic systemic inflammatory arthritis that affects 0.8% of the UK population. RA has a considerable impact on health and socioeconomics as a result of of hospitalisation and loss of employment, with over 50% of patients work-disabled within 10 years of diagnosis. The National Institute for Health and Care Excellence (NICE)'s guidance recommends commencement of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) on diagnosis, usually methotrexate (MTX) and/or additional csDMARDs. If patients fail to respond to these and demonstrate high disease activity [i.e. Disease Activity Score of 28 joints (DAS28) of > 5.1], NICE recommends the use of biologic disease-modifying antirheumatic drugs (bDMARDs). Four different classes of bDMARD are available. Tumour necrosis factor inhibitor (TNFi) (of which there are five different drugs) is the most commonly used. However, up to 30–40% of patients fail to respond or lose an initial response to this bDMARD. In this setting, of the other three classes of bDMARD available, NICE recommends use of only rituximab, which not all patients respond to. This guidance thus limits the use of other potentially effective treatments (alternative TNFi, abatacept and tocilizumab) and is in the absence of any direct trial comparisons.

The ambition of the SWITCH randomised trial was to deliver a definitive trial that would be a paradigm shift in the RA community, delivering the largest RA pragmatic trial undertaken in the UK and thus also establishing a UK-wide research network on which to build future studies. The specific aim of the SWITCH trial was to provide clear guidance on successive bDMARD use to clinicians by assessing whether or not alternative class bDMARDs were comparable in efficacy and safety outcomes with rituximab, the NICE-preferred second-line option. The results of this study were expected to contribute to the development of a treatment algorithm for clinically effective and cost-effective management, in particular to inform individualised treatment regimens as opposed to a blanket switching of all patients to a single (and potentially unsuccessful and toxic) therapy.

Objectives

The primary objective was to determine whether or not an alternative-mechanism TNFi or abatacept (Orencia®; Bristol-Myers Squibb, New York City, NY, USA) was non-inferior to rituximab (MabThera; Roche, Basel, Switzerland) in disease response at 24 weeks post randomisation in patients with RA who had failed to respond to an initial TNFi and concomitant MTX (because of inefficacy).

The secondary objectives were to compare alternative TNFi and abatacept with rituximab with respect to disease response, quality of life, toxicity and safety over 48 weeks; to undertake an evaluation of the cost-effectiveness of switching patients to alternative TNFi (abatacept or rituximab); and, finally, to compare structural and bone density outcomes for abatacept and alternative TNFi to rituximab over 48 weeks using plain radiography and bone densitometry score.

Exploratory objectives were to determine the optimal sequence of treatments by assessing whether or not the response to the second treatment in patients with RA is affected by which of the initial TNFi groups the patients failed, to evaluate if the response to the second treatment is affected by whether or not the patient was a primary or secondary response failure to their initial TNFi therapy and, finally, to ascertain whether or not seropositive [to either or both of rheumatoid factor (RF) and anti-citrullinated peptide antibody (ACPA)] and seronegative (RF and ACPA negative) RA patients behave differently in their response and disease outcome measures in the three treatment arms. These exploratory objectives represented more unique aspects of the trial that held particular clinical relevance.

Methods

Design

The SWITCH study was a multicentre, Phase III, open-label, non-inferiority, three-arm randomised controlled trial comparing the clinical effectiveness and cost-effectiveness of alternative TNFi and abatacept with that of rituximab in patients with RA who have failed to respond to an initial TNFi drug (with concomitant MTX).

Patients were randomised (1 : 1 : 1) to receive alternative TNFi [etanercept (if initial treatment with a monoclonal antibody failed) or a monoclonal antibody of the clinician's choice (if initial treatment with etanercept failed)], abatacept or rituximab (and concomitant MTX), via a minimisation programme incorporating a random element, with minimisation factors centre, disease duration, non-response category seropositive/negative status. Patients received randomised treatment during the interventional phase to a maximum of 48 weeks and were then subsequently followed up to a maximum of 96 weeks in the observational phase.

Setting

The study took place in outpatient rheumatology departments in 35 hospitals throughout the UK.

Participants

Patients diagnosed with RA who were receiving MTX, had not responded to at least two csDMARD therapies, including MTX, and had experienced inadequate response to treatment with one TNFi; these eligibility criteria were based on the NICE and British Society of Rheumatology (BSR)'s guidelines on the use of first-line TNFi.

Interventions

Rituximab (control) is a genetically engineered chimeric (human–murine) monoclonal antibody against the B-cell protein marker CD20.

Abatacept is a selective T-cell co-stimulation blocking agent that is a fusion protein composed of the Fc region of the immunoglobulin G1 (IgG1) fused to the extracellular domain of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4).

Alternative TNFi was etanercept (Enbrel®; Pfizer, New York City, NY, USA) [a human TNF receptor–p75Fc fusion protein produced by recombinant deoxyribonucleic acid (rDNA) technology] or a TNF monoclonal antibody. The specific monoclonal antibodies used were at the discretion of the treating clinician but they were restricted to one of adalimumab (HUMIRA®; Abbott, now AbbVie, North Chicago, IL, USA) (a recombinant fully human IgG1 monoclonal antibody specific for TNF), certolizumab pegol (CIMZIA®; UCB, Brussels, Belgium) [a recombinant (Fc-free) humanised antibody Fab' fragment against TNF and conjugated to polyethylene glycol], infliximab (REMICADE®; Janssen Pharmaceutical, Beerse, Belgium) (a chimeric human–murine IgG1 monoclonal antibody produced by rDNA technology) or golimumab (SIMPONI®; Janssen Pharmaceutical) (a fully human IgG1 monoclonal antibody to TNF).

Outcome measures

The primary outcome measure was the absolute reduction in DAS28 at 24 weeks post randomisation. DAS28 is a composite score calculated as a function of the number of tender and swollen joints, the erythrocyte sedimentation rate and the patient's global assessment of their arthritis.

Secondary outcome measures over 48 weeks were additional measures of disease activity [a reduction in DAS28 of ≥ 1.2, low disease activity rate and remission rate, European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) response, ACR/EULAR Boolean remission, Clinical Disease Activity Index and Simplified Disease Activity Index] and patient-reported outcome measures [Rheumatoid Arthritis Quality of Life (RAQoL), Hospital Anxiety and Depression Scale (HADS), Health

Assessment Questionnaire Disability Index (HAQ-DI) and global assessment of pain, arthritis and general health using visual analogue scales]. The outcomes required for the cost-effectiveness analysis were the EuroQol 5 Dimensions, 3 levels (EQ-5D-3L), and health- and social-care resource use attributable to RA. In addition, radiographic outcome measure and bone densitometry T-scores of the neck of femur and lumbar spine were included. Further outcomes related to safety (adverse events and reactions) and toxicity (requiring cessation of treatment) were reported throughout the trial treatment.

Sample size

A total of 477 patients was required for the sample to have 80% power for demonstrating non-inferiority, at 95% confidence, of either abatacept or alternative TNFi to rituximab in the mean reduction in DAS28 at 24 weeks post randomisation, assuming a non-inferiority limit of –0.6 units, no difference between treatment groups, a between-patient standard deviation (SD) of 1.8 units and loss to follow-up of 10%.

Analysis

An analysis of the primary outcome measure was completed for the intention-to-treat (ITT), per protocol (PP) and complete-case populations. Non-inferiority was defined as the lower limit of the 95% confidence interval (CI) lying above –0.6 units in both the ITT and PP populations. An analysis of secondary outcome measures was undertaken on the ITT and complete-case populations as appropriate. Safety data are summarised on the safety population.

Multiple imputation by chained equations was used to impute missing values at the component level for the DAS28 and American College of Rheumatology 20 (ACR20), under the assumption that the data were 'missing at random'. Parameter estimates across each of the fully imputed data sets were combined using Rubin's rules.

A mixed-effects linear regression model was fitted to the primary outcome measure with covariates corresponding to the minimisation factors and treatment group. Centre was fitted as a random effect.

Covariance pattern models were fitted to the DAS28 and the binary marker (logit link) of a reduction in DAS28 of ≥ 1.2 units over time with covariates entered for the minimisation factors (excluding centre), baseline DAS28, treatment group, time and time-by-treatment interaction. A logistic regression model was fitted to the ACR20 at 24 weeks post randomisation, with covariates entered for the minimisation factors (excluding centre) and treatment group. All additional secondary outcome measures, including further measures of disease activity and quality of life, the exploratory subgroup analyses to evaluate the treatment modification effect of RF/ACPA status, non-response category and initial TNFi group failed on and DAS28 at 24 weeks, are summarised by treatment group and compared informally using descriptive statistics. In addition, treatment compliance, toxicity and safety were summarised.

For the primary cost-effectiveness analysis, total cost and quality-adjusted life-years (QALYs) over the 48-week time horizon and corresponding incremental cost-effectiveness ratios (ICERs) were calculated for each treatment group. For the secondary analysis, a wider cost perspective was adopted to include the total costs incurred by patients.

Results

Between July 2012 and December 2014, when the trial was stopped, 149 patients in 35 centres were registered in the trial, of whom 122 were randomised to treatment.

Comparing alternative TNFi with rituximab, the difference in mean reduction in DAS28 at 24 weeks post randomisation was 0.3 (95% CI –0.45 to 1.05) in the ITT population and –0.58 (95% CI –1.72 to 0.55) in the PP population.

The corresponding results for the comparison of abatacept and rituximab were 0.04 (95% CI –0.72 to 0.79) in the ITT population and –0.15 (95% CI –1.27 to 0.98) in the PP population.

There was evidence of a statistically significant difference in DAS28 at week 36 ($p = 0.022$) between alternative TNFi and rituximab, with a lower DAS28 in the TNFi arm, but this difference was not maintained at week 48. There was no evidence of a clinically or statistically significant difference in DAS28 for abatacept compared with rituximab at any time point. There was no statistically significant difference in the odds of achieving a DAS28 response (i.e. reduction of ≥ 1.2) for either intervention compared with rituximab at any of the time points. Moreover, there was no evidence of a difference in the odds of achieving an ACR20 response at 24 weeks post randomisation for either intervention relative to rituximab.

Overall, a general improvement in HAQ-DI, RAQoL and the patients' general health was apparent over time, with no notable differences between treatment groups. There was a marked initial improvement in the average global assessment of pain and arthritis at 12 weeks for all three treatment groups. Small improvements in the HADS scores sustained over the 48-week period were observed for alternative TNFi and abatacept, whereas no notable improvement was apparent for rituximab.

Ten serious adverse events (SAEs) were reported in nine patients, of which three events in three patients were considered to be related to trial medications. No suspected unexpected serious adverse reactions were reported. Two patients died, both following the development of a SAE (rituximab, abatacept), one of which was a suspected serious adverse reaction (abatacept). Ten patients experienced toxicity resulting in a permanent cessation of treatment (four patients on alternative TNFi, two on abatacept and four on rituximab).

The health economic analysis suggested that switching to alternative TNFi may be cost-effective compared with rituximab [mean cost alternative TNFi, £9680.23 (SD £1263.71); mean cost rituximab, £9367.27 (SD £3215.13); mean QALY alternative TNFi, 0.52 (SD 0.14); mean QALY rituximab, 0.46 (SD 0.18); ICER, £5332.02 per QALY gained]; however, switching to abatacept compared with switching to alternative TNFi is unlikely to be cost-effective [mean cost abatacept, £13,475.09 (SD £4173.22); mean QALY abatacept, 0.53 (SD 0.17); ICER, £253,367.96] when considered against the NICE cost/QALY acceptance threshold of £20,000. The value of information analysis indicated that it would be highly valuable to the NHS to reduce the current uncertainty regarding the effectiveness of alternative TNFi compared with rituximab in the management of RA.

Conclusions

Implications for health care

The clinical question of whether or not alternative bDMARDs and rituximab are comparable in efficacy and safety outcomes in patients with RA who had not responded adequately to an initial TNFi bDMARD and MTX remains unresolved. The lack of evidence, which is based on a single treatment (rituximab) being appropriate for all patients, limits guidance options.

Had the study been extended to enable recruitment to target, definitive evidence on whether or not either of the interventions were non-inferior to rituximab may have been provided, which may have opened up further treatment options for patients.

Trial registration

This trial is registered as ISRCTN89222125 and NCT01295151.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.236

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the Clarivate Analytics Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

The HTA programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: http://www.nets.nihr.ac.uk/programmes/hta

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 08/116/75. The contractual start date was in April 2011. The draft report began editorial review in September 2016 and was accepted for publication in February 2017. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).